## REMARKS

Reconsideration of the present application is respectfully requested in view of the above amendments and the following remarks. Claims 43-50 are currently pending and under examination in the application. However, it should be noted that while Applicants filed new claims 49 and 50 with the last response no mention is made of these claims in the present action. Applicants assume that this was a mere oversight. Accordingly, Applicants are of the position that previously presented claims 49 and 50 are pending, but rejected as being based upon a rejected base claim. Applicants welcome the examiner's comment on claims 49 and 50. Without acquiescence, claim 43 is amended to correct an obvious typographical error. No new matter has been added by the amendment. Support for the amendment can be found in the claims as originally filed.

### CLAIM OBJECTIONS

The Examiner objected to claim 43 for the incorrect spelling of "papveretum," which should be spelled "papaveretum."

Applicants kindly thank the Examiner for pointing out this inadvertent spelling error, and note that claim 43 as amended recites "papaveretum." The Examiner is respectfully requested to withdraw this objection.

### REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The Examiner rejected claims 43-48 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner asserts that the pharmaceutically acceptable derivatives, homologs, or analogs of the recited opioids are not adequately described.

Applicants traverse this rejection and submit that the instant claims comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Written description is adequate when the specification describes the claimed embodiments in sufficient detail to convey *to a person skilled in the art* that the Applicants were in possession of the claimed embodiments at the time of filing, even if each and every species encompassed by the claims is

not *explicitly* described in the specification. *See, e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) citing *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989) ("Although [the applicant] does not have to describe exactly the subject matter claimed, … the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.").

As suggested by *Vas-Cath*, applying a rigid framework would *not* be appropriate when ascertaining whether a particular written description is sufficient. The Federal Circuit Court of Appeals has articulated that with respect to the biological art, "[p]recedent illustrates that the determination of what is needed in a specification to support generic claims related to biological subject matter depends on a variety of factors, including existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter" (*Capon v. Eshhar,* 418 F.3d 1349, 1359 (Fed. Cir. 2005), citing *In re Wallach*, 378 F.3d 1330, 1333-34 (2004); *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004); *Singh v. Brake*, 317 F.3d 1334, 1343 (Fed. Cir. 2003); *see also* M.P.E.P. § 2163.02).

Therefore, the fundamental factual inquiry in determining adequacy of the written description focuses on the understanding of *a person skilled in the art* and whether *a person skilled in the art* would understand that Applicants were in possession of the claimed embodiments. *See also* M.P.E.P. § 2163.02. From this perspective, the instant specification describes the claimed subject matter to a person skilled in the art using sufficiently detailed, relevant identifying characteristics such as *functional characteristics*, and correlating those functional characteristics with the *disclosed structure*. *See Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964, 967, 968 (Fed. Cir. 2002). Under this standard, even a small number of species may adequately describe a genus, so long as the disclosure sets forth adequate details regarding the relevant characteristics of the genus.

As disclosed in the specification and known in the art, persons skilled in the art recognize the *structural* features of "pharmaceutically acceptable derivatives, homologs, or analogs" of the recited opioids. For instance, most generally, persons skilled in the art understand that "derivatives" of a reference compound arise from the replacement of one atom

with another atom or group of atoms, and contain the essential elements of the reference compound (*see, e.g.,* http://www.chemicool.com/definition/derivative.html), conveying a reasonably straightforward chemical relationship between the recited opioids and their derivatives. Also, the specification discloses that "pharmaceutically acceptable derivatives, homologs or analogs" of the recited opioids include pharmaceutically acceptable tautomers, salts, pro-drugs, hydrates, solvates, metabolites, and esters (*see, e.g.,* page 16, lines 25-27 of the specification), thereby describing more particularly the structural features of the encompassed compounds. As disclosed in the specification, it is respectfully submitted that tautomers, salts, pro-drugs, hydrates, solvates, esters, etc. represent structurally well-known chemical variants of a given reference compound, including the recited opioids (*see, e.g.,* page 17, lines 3-31). Thus, from this description, combined with the knowledge in the art, the specification reasonably conveys to persons skilled in the art the *structural features* of the recited opioids and derivatives thereof

In addition, the specification correlates the structural features of the recited opioids, including derivatives, analogs, or homologs thereof, with the disclosed functional features of these compounds. *See Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964, 967, 968 (Fed. Cir. 2002). For example, the opioids and derivatives thereof encompassed by the instant claims function as a full or at least partial agonist of an opioid receptor (*see, e.g.,* page 16, lines 12-14 of the instant specification). In this regard, the claimed opioids are capable of providing (directly or indirectly) the compound concerned or an *analgesically* active compound, metabolite or residue thereof (*see, e.g.,* page 16, lines 27-29), *i.e.,* these compounds are capable of providing an *analgesic response*. Persons skilled in the art understand an *analgesic response* to mean a state of *reduced sensibility to pain*, which preferably occurs without overt sedation and preferably without an effect upon the sense of touch (*see, e.g.,* page 13, lines 17-19 of the specification). Thus, pharmaceutically acceptable derivatives, analogs, and homologs of the recited opioids not only possess the disclosed structural features, as noted above, but are capable of reducing sensibility to pain, a physiological response that is well-understood by those skilled in the art.

Given such a well-understood functional feature, and given also the correlation of this functional feature to the disclosed structural features of the recited opioids and derivatives, analogs, and homologs thereof, it is respectfully submitted that the specification describes the claimed pharmaceutically derivatives, analogs, and homologs of the claimed opioids with sufficient, relevant, identifying characteristics to convey to persons skilled in the art that Applicants possessed the claimed embodiments at the time the application was filed.

Nonetheless, without acquiescence, and solely to expedite prosecution of certain embodiments of Applicants' invention, the recitation "pharmaceutically acceptable derivates, homologs or analogs thereof" has been deleted from claim 43, rendering moot this rejection. Therefore, Applicants submit that the instant claims comply with the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that this rejection be withdrawn.

**REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, INDEFINITENESS**

The Examiner rejected claims 44-47 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Examiner asserts that there is insufficient antecedent basis for the recitation "the flupirtine" in claims 44, 46, and 47.

Applicants traverse this rejection and submit that the instant claims satisfy the requirements of definiteness. Applicants submit that lack of *explicit* antecedent basis for terms does not always render a claim indefinite, especially if the scope of a claim is reasonably ascertainable by those skilled in the art. *See* M.P.E.P. § 2173.05(e), citing *Energizer Holdings Inc. v. Int'l Trade Comm'n,* 435 F.3d 1366 (Fed. Cir. 2006). Here, antecedent basis for the recitation "the flupirtine" is clearly provided by the structure of claim 1, which a person skilled in the art understands to be flupirtine. In this regard, it is respectfully submitted that the scope of the instant claims is reasonably ascertainable by those skilled in the art.

Applicants submit that the instant claims satisfy the requirements of definiteness, and respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

**REJECTIONS UNDER 35 U.S.C. § 102**

The Examiner rejected claims 43-45 and 48 under 35 U.S.C. § 102(e) for alleged lack of novelty over Klose *et al.* (U.S. Patent No. 6,916,486). The Examiner asserts that Klose *et al.* teach an analgesic compound for treatment of neuropathic pain comprising flupirtine and other opioid analgesics. Essentially, the Examiner asserts that the presently claimed combination of flupirtine and other recited opioids is anticipated by claims 11 and 12 of Klose *et al.*, which allegedly recite administering at least one analgesic selected from a list of opioids that includes flupirtine and others.

Applicants traverse this rejection and submit that the instant claims satisfy the requirements of novelty in view of Klose *et al.* Embodiments of the instant claims relate, in pertinent part, to methods for inducing an analgesic response to neuropathic pain, said method comprising administering flupirtine in combination with a recited opioid.

For one, Applicants submit that Klose *et al.* is not enabling for the use of flupirtine as described and claimed therein, especially for the treatment of neuropathic pain. It is respectfully submitted that the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). In this regard, Applicants recognize that issued patents are presumed valid, which includes the presumption of operability *(Metropolitan Eng. Co. v. Coe*, 78 F.2d 199, 25 USPQ 216 (D.C.Cir. 1935). However, affidavits or declarations attacking the operability of a patent cited as a reference may rebut the presumption of operability if they show by a preponderance of the evidence that the patent is not operable. *In re Sasse*, 629 F.2d 675 (CCPA 1980).

Here, Applicants submit for the Examiner's consideration the Declaration of Michael Stephen Roberts, Ph.D (the "Roberts Declaration") as evidence that Klose *et al.* is not enabled for the treatment of neuropathic pain, as presently claimed. Based not only on analysis of the data from Klose *et al.* and products related to that disclosure, but also on estimates using the most widely known skin penetration algorithm, the Roberts Declaration evidences that transdermal delivery of flupirtine, as allegedly disclosed in Klose *et al.*, would fail to provide

adequate blood levels of flupirtine to have any significant effect on neuropathic pain (*see, e.g.,* Items 7-12 of the Roberts Declaration). Dr. Roberts, thus, concludes that it is not technically possible to apply the art defined by Klose *et al.* to enable an adequate transdermal delivery of flupirtine to achieve the recommended daily doses of 200mg or 300mg to 600mg for central analgesia in the treatment of neuropathic pain (*see, e.g.,* Item 13 of the Roberts Declaration). Given this evidence, it is respectfully submitted that the passing mention in Klose *et al.* that the agents described therein can be used for neuropathic pain does not enable the specific use of flupirtine for such treatments, as relied upon by the Examiner, let alone does it enable the specific use of flupirtine in combination with an opioid for the same, as presently claimed. Therefore, Applicants submit that the disclosure in Klose *et al.* is inadequate to anticipate the instant claims.

Nonetheless, even assuming, *arguendo*, that the disclosure Klose *et al.* is enabled for the reasons relied upon by the Examiner, this reference fails to anticipate the subject matter of the instant claims. Particularly, Applicants note that in order to anticipate the claims, the claimed subject matter must be disclosed in the reference with '*sufficient specificity*' to constitute an anticipation under the statute. M.P.E.P. § 2131.03 (*emphasis added*). It is not enough to disclose all the claim elements, rather "[t]he identical invention must be *arranged* as required by the claim..." *Id.* (without internal citations) (emphasis added). Here, Klose *et al.* fail to disclose with *sufficient specificity* the specific combination of flupirtine and the recited opioids for treating neuropathic pain.

Klose *et al.* fail to specifically disclose the specific combination of flupirtine and the recited opioids for treating neuropathic pain. To the contrary, claims 11 and 12 of Klose *et al.*, at best, represent a genus-like disclosure of a list of individual analgesics, which does not necessarily anticipate claims to a specifically selected combination (*i.e.,* species) of analgesics (*see, e.g., Integra Lifesciences v. Merck*, 331 F.3d 860, 869 (Fed. Cir. 2003) ("[G]enus patents do not estop the applicant from later filing an improvement patent...to claim species with *particularly useful properties*)(emphasis added)), especially, as is the case here, when this combination has been demonstrated by Applicants to have unexpectedly synergistic effects over standard treatment methods for neuropathic pain (*see, e.g.,* page 45, lines 4-16 of the

specification). Indeed, other than the general, boilerplate claim preamble language relied upon by the Examiner (*i.e.,* "at least one"), Klose *et al.* contain nothing to suggest or even remotely contemplate the use or benefits of *any* combination of opioids to provide a synergistic effect in treating neuropathic pain, let alone the specific combination of flupirtine and the recited opioids of claim 43. In the present case, it is respectfully submitted that because the standard claim drafting tool "at least one" does not rise to the level of an anticipatory disclosure with regard to such a specifically claimed combination, Klose *et al.* fail to disclose the subject matter of the instant claims with *sufficient specificity* to constitute an anticipation under section 102.

Since Klose *et al.* not only fail to disclose the claimed subject matter with *sufficient specificity* to be anticipatory under section 102, but fail to adequately enable the use of flupirtine for the purposes disclosed therein, Applicants submit that the instant claims are novel, and respectfully request withdrawal of this rejection under 35 U.S.C. § 102(e).

**REJECTIONS UNDER 35 U.S.C. § 103**

A. The Examiner rejected claim 47 under 35 U.S.C. § 103(a) for alleged obviousness over Klose *et al.* in view of Devulder *et al.* The Examiner agrees that Klose *et al.* fail to teach the dosage range recited in claim 47, but asserts that Devulder *et al.* teach a flupirtine dosage range that fails within the claimed range. The Examiner, thus, asserts that the it would have been obvious to utilize the dosage range of Devulder *et al.* in the method of Klose *et al.*

B. The Examiner rejected claim 46 under 35 U.S.C. § 103(a) for alleged obviousness over Klose *et al.* in view of Perovic *et al.* The Examiner agrees that Klose *et al.* fail to disclose the absence of overt sedation of opioids in the presence of flupirtine. The Examiner asserts, however, that Perovic *et al.* teach that flupirtine rarely causes drowsiness, and further asserts that since the claims encompass an almost negligible amount of opioid, such overt sedation would obviously not occur since it is dose related.

Applicants traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness over any combination of Klose *et al.* in view of Devulder *et al.*

or Perovic *et al.* Specifically, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness).

It is respectfully submitted that Klose *et al.*, alone or in combination with Devulder *et al.* Perovic *et al.*, fail to teach, suggest, or motivate a person skilled in the art to use flupirtine *in combination* with the recited opioids for treating neuropathic pain with any expectation of success, let alone with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art"). To the contrary, as noted above, other than the generalized, boilerplate claim preamble language relied upon by the Examiner (*i.e.,* "at least one"), Klose *et al.* contain nothing to suggest that this reference even remotely contemplates the benefits of any combination of opioids, let alone the *specific* combination of flupirtine and the recited opioids of independent claim 43. In this regard, persons skilled in the art would have to embark on a whole new line of experimentation, such as that performed by Applicants, to arrive at the understanding that flupirtine *in combination* with the recited opioids provides unexpected synergistic effect in treating the particular problems associated with neuropathic pain (*see, e.g.,* page 45, lines 4-16 of the specification). The suggestion or motivation for such a new line of experimentation cannot be found in any of Klose *et al.*, Devulder *et al.*, or Perovic *et al.*

On this point, Applicants submit that assertions of obviousness, such as those to support a reasonable expectation of success, can not be based on generalized teachings, but must be based on articulated, technical reasoning. *See KSR v. Teleflex, Inc.* at 14, citing *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere *conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.") (emphasis added). Given the absence of such technical reasoning or evidence on the expectations of utilizing the *specific combination* of flupirtine and a recited opioid for treating neuropathic pain, Applicants submit that the cited references, alone or in combination, fail to provide a *prima facie* case of

obviousness, since these references fail to fairly teach or suggest each feature of independent claim 43, let alone those dependent therefrom, and further fail to provide any motivation to practice the recited subject matter with a reasonable expectation of success.

Further, with regard to the rejection of claim 46 over the combination of Klose *et al.* and Perovic *et al.*, Applicants respectfully disagree with the Examiner's reliance on Perovic *et al.* in asserting that flupirtine was considered to cause drowsiness in only 10% of cases (*see* page 373, column 2, last paragraph of Perovic *et al.*). Rather, a closer look reveals that this statement in Perovic *et al.* is not supported by any real evidence. Specifically, Perovic *et al.* cite McMahon *et al.* (*Postgraduate Medical Journal* 63:81-85, 1987, submitted herewith) for the assertion that flupirtine was reported to cause drowsiness in only 10% of cases. However, McMahon *et al.* further cite Hlavica *et al.* (*Arzneimittelforschung* 35:67-74, 1985, English translation submitted herewith) as evidence this specific result (*see, e.g.,* page 84, column 2, paragraph 2, Discussion, paragraph 2, last sentence of McMahon *et al*). The problem is that Hlavica *et al.* not only make no mention of flupirtine causing drowsiness in only 10% of cases, but the results contained therein do not compel any such conclusion. Also, McMahon *et al.*, relying on their own data, teach that drowsiness is the most common adverse experience subsequent to administration of flupirtine (*see, e.g.,* page 84, column 2, first paragraph), though the specific relevance of these studies to the instant claims is questionable, given that the treatment of neuropathic pain typically requires longer-term exposure to analgesics, and McMahon *et al.* merely measure the effects of flupirtine following an acute exposure. In fact, it is fair to expect the potential for adverse effects to be higher for the types of longer-term therapies appropriate to the treatment of neuropathic pain, as presently claimed, evidencing the unexpected nature of the results described by Applicants, wherein opioids do not induce overt sedation in the presence of flupirtine.

Also with regard to Perovic *et al.,* Applicants respectfully disagree with the Examiner's assertion that the instant claims read on "negligible" amounts of opioids. Rather, the instant claims recite that the claimed compounds are administered in an "*amount effective* to reduce the level of or to otherwise ameliorate the sensation of pain," which necessarily precludes the use of negligible amounts of opioids. In view of this understanding, as well as the limitations

of Perovic *et al.* discussed above, Applicants submit that it would not have been obvious to employ a non-sedating dose of flupirtine and an opioid, as recited in claim 46.

In addition, the non-obviousness of the instant claims, including independent claim 43, is supported by secondary considerations, such as improved properties and unexpected results. *See, e.g., In re Dillon,* 919 F.2d 688, 692, 693 (Fed. Cir. 1990). Also, it is respectfully submitted that synergism may point toward non-obviousness. *See* M.P.E.P. § 2141(I). Here, as noted above, it was unexpected to find that the combination of flupirtine and an opioid *synergistically* reduces pain symptoms (*see, e.g.,* page 45, lines 4-16 of the specification), thereby allowing the use of *reduced levels* of opioids during neuropathic pain therapy. This unexpected benefit alone is therapeutically significant in the treatment of neuropathic pain, because the use of opioids is often frequent and sustained due to the diminished effects of opioids in subjects suffering from neuropathic pain. Such over use is often associated with addiction, the development of tolerance, and an increase in the number and severity of side effects associated with opioid use (*see, e.g.,* page 4, lines 8-11). Among other benefits, these synergistic effects allow those undergoing neuropathic pain management therapy to reduce the risk of tolerance, avoid the life-interfering effects of overt sedation (*see, e.g.,* page 14, lines 23-29), as well as manage other side effects, including euphoric effects, emetic effects, spastic constipation and increased smooth muscle tone (*see, e.g.,* page 4, lines 11-12). Therefore, the unexpected synergistic results demonstrated by Applicants provide real-world benefits in neuropathic pain therapy, and clearly support the non-obviousness of the instant claims.

In view of the above remarks and the evidence provided herein, Applicants submit that the instant claims satisfy the requirements of non-obviousness under 35 U.S.C. § 103(a), and respectfully request withdrawal of this rejection.

Applicants believe that all of the claims in the application are allowable. However, should the Examiner believe that the claims are not in condition for allowance, she is respectfully requested to telephone the undersigned to resolve any outstanding issues. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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Enclosures:

Declaration of Michael Stephen Roberts, Ph.D.
Curriculum Vitae of Michael Stephen Roberts, Ph.D.
McMahon *et al.*, *Postgraduate Medical Journal* 63:81-85, 1987.
Hlavica *et al.*, *Arzneimittelforschung* 35:67-74, 1985, English translation.

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